

**Amendments to the Claims**

Please **cancel** Claims 2 through 5, 7, 8 and 11 through 20. Please **amend** Claim 1 as indicated below in the listing of claims. Please **add** new Claims 21 through 46 as presented below.

**Listing of Claims**

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A method for ameliorating neuronal atrophy and loss accompanying aging in the mammalian brain, the method comprising ~~directly or indirectly~~ delivering ~~a unit dosage of~~ a neurotrophin-encoding transgene composition to preselected delivery sites in the brain for expression of neurotrophin at, or within diffusion distance of, targeted neurons, wherein the ~~encoded~~ growth factor stimulates non-chemotropic growth by, or activity in, the targeted neurons, and ~~stimulates axonal growth in targeted growth factor-receptive neurons therein.~~
2. (Cancelled)
3. (Cancelled)
4. (Cancelled)
5. (Cancelled)

6. (Withdrawn) The method according to Claim 1, wherein the neurotrophin-encoding transgene composition is delivered indirectly, from grafts of transgene-secreting donor cells introduced into the brain.
7. (Cancelled)
8. (Cancelled)
9. (Withdrawn) The method according to Claim 6, wherein the donor cells are delivered in a pharmaceutically acceptable composition having a concentration of at least  $1 \times 10^5$  donor cells/ $\mu$ l.
10. (Withdrawn) The method according to Claim 9, wherein each graft contains from 2 to 20  $\mu$ l of the donor cell containing composition.
11. (Cancelled)
12. (Cancelled)
13. (Cancelled)
14. (Cancelled)
15. (Cancelled)
16. (Cancelled)
17. (Cancelled)
18. (Cancelled)

19. (Cancelled)

20. (Cancelled)

21. (New) The method according to Claim 1, wherein the targeted neurons are cholinergic neurons.

22. (New) The method according to Claim 21, wherein the stimulation occurs in a cortical region of the brain.

23. (New) The method according to Claim 22, wherein each delivery site is preselected by correlating sites of potential loss of cortical fiber density to potential impairment of neurological function in the aging brain.

24. (New) The method according to Claim 23, wherein the cortical region of the brain is the insular or temporal cortex.

25. (New) The method according to Claim 22, wherein the stimulation occurs in the cingulate, frontal, entorhinal or hippocampal cortices.

26. (New) The method according to Claim 21, wherein the stimulation occurs in the cholinergic forebrain.

27. (New) The method according to Claim 22 or 26, wherein the region of the brain containing the targeted neurons is the striatum.

28. (New) The method according to Claim 26, wherein the treated mammal is a human with Alzheimer's Disease.

23. (New) The method according to Claim 22, wherein each delivery site is preselected by correlating sites of potential loss of cortical fiber density to potential impairment of neurological function in the aging brain.

24. (New) The method according to Claim 23, wherein the cortical region of the brain is the insular or temporal cortex.

25. (New) The method according to Claim 22, wherein the stimulation occurs in the cingulate, frontal, entorhinal or hippocampal cortices.

26. (New) The method according to Claim 21, wherein the stimulation occurs in the cholinergic forebrain.

27. (New) The method according to Claim 22 or 26, wherein the region of the brain containing the targeted neurons is the striatum.

28. (New) The method according to Claim 26, wherein the treated mammal is a human with Alzheimer's Disease.

29. (New) The method according to Claim 1, wherein the targeted neurons are dopaminergic neurons.

30. (New) The method according to Claim 29, wherein the stimulation occurs in the substantia nigra.

31. (New) The method according to Claim 30, wherein the region of the brain containing the targeted neurons is the striatum.

32. (New) The method according to Claim 29, wherein the treated mammal is a human with Parkinson's Disease.

33. (New) A method for stimulating neuronal growth and activity in the mammalian brain, the method comprising delivering a neurotrophin-encoding transgene composition to a region of the brain having targeted neurons therein, wherein the expressed growth factor stimulates growth by, or activity in, neurons in another region of the brain.

34. (New) The method according to Claims 1 or 33, wherein the growth factor-encoding transgene composition is delivered directly, by introduction of a transgene-expressing recombinant expression vector into the preselected delivery sites.

35. (New) The method according to Claim 34, wherein the transgene-expressing recombinant expression vector is a viral vector.

36. (New) The method according to Claim 35, wherein the viral vector is delivered in a pharmaceutically acceptable composition, and provides from  $10^{10}$  to  $10^{12}$  viral particles/ml of composition.

37. (New) The method according to Claims 1 or 33, wherein the mammal is a human and the transgene encodes a human nervous system growth factor.

38. (New) The method according to Claim 37, wherein the transgene encodes nerve growth factor (NGF).

39. (New) The method according to Claim 1, wherein the transgene encodes neurotrophin 3 (NT-3).

40. (New) The method according to Claim 37, wherein the transgene encodes glial derived nerve growth factor (GDNF).
41. (New) The method according to Claim 1, wherein the transgene encodes neurturin.
42. (New) The method according to Claim 1, wherein the transgene encodes neurotrophin 4/5 (NT-4/5).
43. (New) The method according to Claim 1, wherein the transgene encodes persephin.
44. (New) The method according to Claim 35, wherein the viral vector is an adeno-associated viral vector.
45. (New) The method according to Claim 35, wherein the viral vector is a lentiviral vector.
46. (New) The method according to Claim 1, wherein the mammal is a human with aging-related impairment.

## REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### A. Overview of the Invention.

The invention provides means for ameliorating the effects of the aging process on the brain. The invention further provides means for increasing axonal density in a region of the brain than is innervated by targeted neurons.

Previous reports (including the inventor's own previously issued patents) have indicated that localized neuronal atrophy can be modulated by treating the neuron with a growth factor. To this end, the growth factor is introduced into the neuron itself, or into the nearby brain tissue. Such growth is considered to be "chemotropic" in nature; i.e., where neurons respond directly, at the site of the treatment, to contact with a growth factor.

However, no previous report has suggested that treating one segment of a neuronal cell with growth factor can stimulate activity or growth in *another* part of the neuron. The invention provides means to stimulate such growth, even when the neuron extends a significant distance from the delivery site; e.g., a region of the brain having delivery sites therein that innervates, or is innervated by, another region of the brain. Such growth is "non-chemotropic" in nature; i.e., it likely occurs through triggering of a signaling pathway or other response in the neuron downstream of the site of contact between the neuron and the growth factor.

Therefore, practice of the invention to deliver a growth factor to the brain provides neuronal growth not only in the treated region of the brain (where a growth factor is delivered), but also in regions of the brain innervated by the treated neurons.

This phenomenon is especially well defined in the Specification at page 7, lines 1-25 (the influence of expressed growth factors on distant regions of the brain is a non-chemotropic phenomenon, possibly involving downstream activation of signaling pathways), and by:

- Example IV herein, wherein *in vivo* delivery of a growth factor expressing vector into the forebrain influenced neuronal growth within the forebrain and cortices.
- The inventor's Declaration under 37 CFR 1.132 submitted herewith, wherein *in vivo* delivery of a growth factor expressing vector into the striatum influenced neuronal growth within the substantia nigra.

**B. Support for Claim Amendments and Additions.**

Claims 2 through 5 are cancelled.

Claims 7 and 8 are cancelled.

Claims 11 through 20 are cancelled.

Claims 6, 9 and 10 were previously withdrawn as drawn to an non-elected invention.

Claims 21 through 46 are added by this amendment.

In view of these amendments, Claims 1 and 21 through 46 are now pending in the application. No new matter has been added to the application by the proposed amendments. In particular, support for the claim limitations now present is found in the Specification as follows:

Claim Number	Amended Claim Limitation	Representative Examples of Specification Support
1	Delivery sites are in "a region of the brain having targeted neurons therein,"	Figure 3; page 6, lines 14-20; page 19, lines 17-20
1	"wherein expression...non-chemotropically stimulates ...."	Page 2, lines 15-20, and page 6, lines 19-30; original claim 16.

Claim Number	Amended Claim Limitation	Representative Examples of Specification Support
1	"...growth by, or activity in, targeted neurons."	Page 2, lines 15-19; page 6, lines 14-20; and page 6, lines 19-30; original claim 16.
21	Targeted neurons are cholinergic neurons.	<i>See</i> , original Claims 1 and 2.
22, 24, 25	Growth or activity may be stimulated in a cortical region of the brain (insular and temporal cortices according to claim 24 and the entorhinal, cingulate, frontal and hippocampal cortices according to claim 25).	<i>See</i> , original Claims 15 and 18; Page 2, lines 15 through 19; page 6, lines 1-13 (insular and temporal), lines 14-20 and lines 19-30.
26	Delivery sites may be in a cholinergic region of the brain.	<i>See</i> , original claims 1, 2, 14 and 17; Figures 1 through 4; page 5, lines 6-16.
29	Targeted neurons may be dopaminergic neurons.	<i>See</i> , original claim 19; page 7, lines 12-24.
30	Stimulation may occur in the substantia nigra.	<i>Id.</i>
27, 31	Targeted neurons may be in the striatum.	<i>Id.</i> , and Tuszynski Declaration.
24	Mammal may be human; transgene may encode a nervous system growth factor.	Original claims 11 and 12.
25	Transgene may be delivered via a viral vector.	Original claim 7.
44	Vector may be an adeno-associated viral vector.	<i>See</i> , original claim 7; page 9, line 31 through 10, line 30.
45	Vector may be a lentiviral vector.	<i>See</i> , original claim 7; page 9, line 31 through 10, line 30.
37, 38, 39, 40, 41, 42, 43	Transgene may encode growth factors such as NGF, NT-3, GDNF, neurturin, persephin and NT-4/5.	<i>See</i> , original claim 11 (growth factors generally), 12 (NGF), 13 (NT-3); page 8, line 22 through page 9, line 19.

Claim Number	Amended Claim Limitation	Representative Examples of Specification Support
28, 32, 46	Treated mammal may be a human with Alzheimer's or Parkinson's Disease, or age-related impairments.	<i>See</i> , original claim 1; page 6, lines 5-30 (aging); page 7, lines 12-24 (AD and PD).
34	Delivery may be <i>in vivo</i> .	<i>See</i> , original claim 5; page 2, lines 8-15; page 14, lines 21-30.
36	Dosing may provide $10^{10}$ to $10^{12}$ viral particles/ml. composition.	<i>See</i> , original claim 8; page 8, lines 6-9.
23	A method for stimulating neuronal growth and activity in the mammalian brain, the method comprising delivering a neurotrophin-encoding transgene composition to a region of the brain having targeted neurons therein, wherein the expressed growth factor stimulates growth by, or activity in, neurons in another region of the brain	<i>See</i> , original claim 16; Figure 3; page 6, lines 14-20; page 19, lines 17-20; page 2, lines 15-20, and page 6, lines 19-30.

No new matter is introduced by these amendments. Entry thereof is therefore requested.

C. Response to Objection to Priority Claim.

In the Office Action, the refusal of Applicant's priority claim to Serial No 09/060,543, now U.S. Patent No. 6,451,306 (the '306 Patent) is continued on the asserted basis that the parent application "fails to disclose a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering a transgene encoding a growth factor to preselected sites in the brain."

However, Applicant respectfully submits that the refusal of the priority claim is rendered in part moot by Applicant's previous amendment to the Specification to recite a priority claim to Applicant's prior U.S. Patent 6,683,058. Reference to the 09/060,543 application is made in the priority claim as identification of the '058 Patent, which is a continuation-in-part of the '543 application. No objection to Applicant's claim of priority to the '058 Patent has been made. Confirmation that the priority claim is granted to the date of the '058 Patent; i.e. July 19, 2000, is requested.

Further, Applicant respectfully maintains that he is entitled to the priority of the '053 application for all subject matter common to it and the present application, under 35 USC Section 120. Under Section 120, it is clear that, in a continuation-in-part application "matter disclosed in the parent application is entitled to the benefit of the filing date of the parent application." *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 32 F.3d 556, 558, 31 USPQ2d 1855, 1857 (Fed.Cir.1994). The benefit of the filing date of an earlier application is accorded for all common subject matter if there is at least one common inventor between the applications, the CIP was filed while the parent application was still pending, and the CIP contains a reference back to the parent application. *See*, MPEP 201.08.

All of these conditions are met in the present application, which contains subject matter common to the disclosure of the '053 application, as set forth in Applicant's Amendment of June 21, 2004. As such, it is respectfully submitted that the priority claim *for subject matter common to the present application and the '053 application* parent should be withdrawn.

D. Response to Objection Against Claims 5, 7 and 8 under Section 112, Second Paragraph

The phrase “growth factor encoding transgene composition has been delivered directly” was objected to as indefinite as not identifying the location to which the composition was delivered. The phrase has been amended where it appears in the newly presented claims to specify that the delivery is to the preselected delivery sites recited in Claim 1. Applicant therefore submits that the objection has been overcome, and requests that it be withdrawn.

E. Response to Rejection of Claims 1-5, 7, 8 and 11-15 under Section 112, First Paragraph.

In essence, the enablement rejection as it is now stated has three parts:

First, a query regarding the fate of the vector and expressed protein once placed into the target tissue. This aspect of the rejection is based on the contention that the art of gene therapy is unpredictable, in so far as the “fate of the DNA vector itself...the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within the cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein’s compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy.” (Office Action, page 4, last paragraph through page 5, first paragraph).

Second, a query regarding the how the vector is placed into the target tissue; i.e., as to the route of administration and transfection efficacy: “Administration route also plays an important role in determining gene transfer efficiency *in vivo*.” (Office Action, page 5, first paragraph).

Third, a query regarding whether the specification adequately teaches expression of the growth factor in a neuron where “the delivery site is remote from the targeted neuron.” (Office Action, page 4, first paragraph).

Of these three issues, the first—what happens to a vector introduced *in vivo* and the protein expressed thereby once they are in the brain?-- was raised, and resolved, during prosecution of the parent application, now U.S. Patent No. 6,683,058.

In particular, the presently elected claims (Claims 1, 5 and 6) extend to *in vivo* administration of an expression vector encoding a growth factor, as is also claimed in the '058 Patent. As was confirmed during prosecution of the '058 Patent, the vectors useful in such administration can be taken up by, and expressed in, neurons in the brain. Expression can persist for many months, without untoward responses to the vector or protein, such as inflammation.

Therefore, to the extent that the enablement rejection raises the same inquiries concerning the fate of an expression vector and expressed growth factor in brain cells that were raised in the '058 Patent, the resolution of the issues in the '058 Patent (i.e., confirming that transfection and expression at a sufficient level to produce a biological response can be achieved by introducing a growth factor-encoding expression vector into brain tissue) applies with equal force in the present application.

In other words, there is no reason to believe that the art would consider the likely fate of a vector administered into a brain cell using the means taught by the present disclosure to be any different now than it was likely to be at the time that the '058 Patent—which discloses essentially the same means for administration of the same vector compositions--was prosecuted. To the contrary, like its parent application, the present disclosure establishes that transfection and persistent expression in brain cells can be achieved. Therefore, this aspect of the enablement rejection has already been addressed and overcome with respect to the uptake, expression and fate, in the brain, of the growth factor-encoding compositions useful in the invention, and should be withdrawn.

With respect to the second aspect of the enablement rejection (as to route of administration), the presently claimed invention differs from previously claimed inventions in

that, according to the present invention, the *effects* of the expressed growth factor may be felt in regions of the brain that are remote from the delivery sites.

It is understood in the art (principally as developed since the filing date of this application) that growth factor expressed in, or taken up by, the cell body of a nerve can be transported intracellularly to distant axonal termini of the nerve, and vice-versa, to exert biological activity in innervated regions of the brain remote from the expression site. In particular, it is now known that growth factors are transported within neuronal cells both in a retrograde direction (into cell nuclei) and an anterograde direction (to axonal termini). *See, e.g.,* Conner, *et al.*, *Proc. Natl. Acad. Sci. USA.*, 98: 1941–1946 (2001)(growth factors expressed at one site in the brain exert trophic influence over growth among neuronal populations in proximal regions of the brain); Curtis, *et al.*, *Mol. and Cell Neurosci.*, 12:105-118 (1998) (retrograde transport of growth factors increases following injury to nerve cells); von Bartheld, *et al.*, *Mol. Neurobiol.*, 24:1-28 (Humana Press, 2001) (anterograde transport of NGF and GDNF family growth factors and transfer thereof from axonal termini to proximal second or third order target cells); and von Bartheld, *et al.*, *Letters to Nature*, 379:830-833 (1996)(anterograde transport and intercellular transfer of NGF family growth factors in the visual nervous system of chicks). Thus, a growth factor expressed in, or taken up by, a neuron at one site may exert influence over growth of by the neuron at a significant distance from that site.

Further, growth factor transport can occur *between cells* via intercellular transport from axonal termini. *See, e.g.,* von Bartheld, *et al.*, *Mol. Neurobiol.*, supra. As such, expression and uptake of a growth factor by a neuron at one segment of the cell (i.e., by neuronal somata [cell bodies], dendrites or axonal termini) can exert influence over activity and growth at another segment of the neuron, even when the uptake site is in a remote region of the brain. As such, delivery of a growth factor according to the invention into a first region of the brain will affect growth and activity of neurons that project into or from that region to another (e.g., from the striatum to the forebrain, from the substantia nigra to the striatum, from the forebrain to the cortices).

For example, see Example IV herein, wherein *in vivo* delivery of a growth factor expressing vector into the forebrain influenced activity and growth in the cortex (into which neurons projected from the forebrain); and in the inventor's co-pending U.S. Patent Application No. 09/730,790 (now US Patent No. 6,815,431), wherein *in vivo* delivery of a growth factor expressing vector into the striatum (into which neurons projected from the substantia nigra) influenced growth within the distant substantia nigra (*see also*, data set forth in the Declaration of Dr. Mark H. Tuszynski, submitted herewith).

However, contrary to the perception stated in the Office Action, neither the present disclosure nor the claims lack sufficient guidance as to the location of the delivery sites utilized in the invention, or the region of the brain affected by expressed growth factor. Instead, the claims quite clearly direct the ordinary artisan to delivery sites that will allow the delivered expression vector to be expressed within diffusion distance of a targeted neuron, which innervates a region of the brain in which a response to the growth factor is desired.

As noted, the inventor was the first to discover that such a “non-chemotropic” impact on growth of neurons can be achieved. This discovery opens up a new vista in treatment of neurological impairments, allowing physicians not only to stimulate growth in regions of the brain to which growth factors are introduced, but to also influence—at the same time—growth in regions of the brain receiving innervation from the treated neurons.

This principle, and the means by which it is applied in practice, are amply demonstrated in the Specification; see, e.g., Page 2, lines 15-20, and page 6, lines 14-30; and Example V. Those of ordinary skill in the art, having the usual level of knowledge concerning the neurological structure of the brain, will have no difficulty identifying regions of the brain that (a) experience a loss of neuronal density or activity in connection with aging or impairment; and, (b) receive innervation by neurons whose loss of function is related to the effects of aging or impairment.

With that information defining the goal of treatment, artisans can readily identify the location of the soma of the targeted neurons (e.g., cholinergic neurons originating in the basal forebrain, dopaminergic neurons originating in the substantia nigra, or cortical neurons) and provide treatment according to the methods of the invention accordingly. Such anatomical and physiological information is well-known and the art, and need not be (indeed, is preferably not<sup>1</sup>) detailed in the Specification for the claims to be enabled. Nonetheless, particular neurons and dysfunctions of interest that are known in the art and amenable to treatment according to the invention are identified in the Specification; e.g., Alzheimer's and other memory impairments (cholinergic neurons); Parkinson's and other tremor impairments (dopaminergic neurons) and, in a preferred embodiment, atrophies related to aging (loss of cortical fiber density) (Specification at page 1, lines 10-26).

Therefore, Applicant respectfully submits that the claims are amply enabled by the Specification with respect to route (location) of administration, and the location of the intended effect of treatment.

Lastly, with respect to the third issue raised (whether the delivery sites can be distant from the targeted neurons), Applicant respectfully disagrees that the claims are only enabled for administration of a expressible growth factor within 500  $\mu\text{m}$  of a targeted neuron.

In one aspect, the *gist* of the present invention is that it provides a method for stimulating growth in a portion of a neuron that is, by definition, remote from the delivery site. As to how close the delivery site must be to the neuron, the Specification makes it clear that the goal is to provide the growth factor at a delivery site that is "at the target site, or within diffusion reach of a chemotropic (concentration) gradient leading to the target site" (Specification at page 7, lines 10-12). The disclosure suggests that the diffusion reach can "generally" be expected to be about 500  $\mu\text{m}$  from the target site (*Id.*), although those of ordinary skill in the art will recognize that the

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<sup>1</sup> "[A] patent application does not need to include in the specification that which is already known to and available to one of ordinary skill in the art." *Koito Mfg. Co. v. Turn-Key-Tech, LLC.*, 381 F.3d 1142, 1156 (Fed. Circ. 2004).

actual diffusion reach of a growth factor may vary somewhat with the condition and morphology of the treated brain tissue, strength of expression achieved, diffusion of the vector from the delivery site, and so forth.

As claimed, however, the distance between the targeted neurons and each delivery site is not critical to the invention. For entirely *chemotropic* stimulation of growth, placing each delivery site within about 500  $\mu\text{m}$  of a targeted neuron enhances the effect of local expression. In contrast, the previously unobserved *non-chemotropic* effects of the invention on axons as presently claimed are not necessarily dependent on the concentration of growth factor at the point of uptake by a targeted neuron, as the neuron itself accomplishes delivery of the growth factor to the segment in which growth and/or activity is to be stimulated. As such, it is not appropriate to limit the scope of protection for Applicant's discovery to delivery sites chosen for a *different* purpose; i.e., for chemotropic stimulation of growth.

For all of the foregoing reasons, Applicant submits that the claims as amended are fully enabled by the Specification. Therefore, reconsideration and withdrawal of the rejection of the claims under Section 112, first paragraph is respectfully requested.

F. Response to Rejection of Claims 1, 5 and 7 Under Section 102(b) Based on Kojima.

The claims are rejected as being anticipated by Kojima, *et al.*, 1997 (Kojima). Applicant respectfully traverses the rejection.

Kojima neither teaches nor suggests the claimed invention for reasons including the following. Nothing in the reference suggests any non-chemotropic response to the hGDNF administered. Further, nothing in the reference suggests any stimulation of growth in response to the hGDNF administered. Indeed, no structural changes in the brain of any kind were noted.

In addition, the reported *in vivo* experiment failed to produce even a chemotropic effect on the one measured criterion, dopamine production (see, page 571, second column, second paragraph).

In contrast, the present invention produces both chemotropic and non-chemotropic changes in protein expression and neuronal growth (see, e.g., Example V), without immunogenic or cytotoxic effects (see, e.g., Example VI). For all of these reasons, the Kojima reference does not anticipate the presently claimed invention.

G. Response to Rejection of Claims under 1, 5, 7 and 8 Under Section 103(a) Based on Mandel, *et al.* (1999) (Mandel)

As noted in the previous Amendment, the critical teachings of the present disclosure are wholly absent from Mandel. For example, nothing in the reference suggests any non-chemotropic response to the NGF administered. Further, nothing in the reference suggests any stimulation of growth in response to the NGF administered. Indeed, similar to the failings of the Kojima reference, no structural changes in the brain of any kind are noted in Mandel, *et al.*

In short, nothing in Mandel would lead one of ordinary skill in the art to suspect that non-chemotropic stimulation of growth (or activity) in a neuron can be achieved by exposure of a distant segment of the neuron to a growth factor-expressing transgene. Therefore, Mandel does not render the claimed invention obvious.

Reconsideration and withdrawal of the rejection of claims under Section 103(a) based on Mandel is therefore respectfully requested.

**CONCLUSION**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date February 18, 2005

By

2-18-2005

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Enclosures: Clean copy of amended claims

**Clean Copy of the Amended Claims**

1. (Currently Amended) A method for ameliorating neuronal atrophy and loss in the mammalian brain, the method comprising delivering a neurotrophin-encoding transgene composition to preselected delivery sites in the brain for expression of neurotrophin at, or within diffusion distance of, targeted neurons, wherein the growth factor stimulates non-chemotropic growth by, or activity in, the targeted neurons.

Claims 2 through 5 are cancelled.

Claim 6 is withdrawn.

Claims 7 and 8 are cancelled.

Claims 9 and 10 are withdrawn.

Claims 11 through 20 are cancelled.

21. (New) The method according to Claim 1, wherein the targeted neurons are cholinergic neurons.

22. (New) The method according to Claim 21, wherein the stimulation occurs in a cortical region of the brain.

23. (New) The method according to Claim 22, wherein each delivery site is preselected by correlating sites of potential loss of cortical fiber density to potential impairment of neurological function in the aging brain.

24. (New) The method according to Claim 23, wherein the cortical region of the brain is the insular or temporal cortex.

25. (New) The method according to Claim 22, wherein the stimulation occurs in the frontal, cingulate, entorhinal or hippocampal cortices.
26. (New) The method according to Claim 21, wherein the stimulation occurs in the cholinergic forebrain.
27. (New) The method according to Claim 22 or 26, wherein the region of the brain containing the targeted neurons is the striatum.
28. (New) The method according to Claim 26, wherein the treated mammal is a human with Alzheimer's Disease.
29. (New) The method according to Claim 1, wherein the targeted neurons are dopaminergic neurons.
30. (New) The method according to Claim 29, wherein the stimulation occurs in the substantia nigra.
31. (New) The method according to Claim 30, wherein the region of the brain containing the targeted neurons is the striatum.
32. (New) The method according to Claim 29, wherein the treated mammal is a human with Parkinson's Disease.
33. (New) A method for stimulating neuronal growth and activity in the mammalian brain, the method comprising delivering a neurotrophin-encoding transgene composition to a region of the brain having targeted neurons therein, wherein the expressed growth factor stimulates growth by, or activity in, neurons in another region of the brain.

34. (New) The method according to Claims 1 or 33, wherein the growth factor-encoding transgene composition is delivered directly, by introduction of a transgene-expressing recombinant expression vector into the preselected delivery sites.

35. (New) The method according to Claim 34, wherein the transgene-expressing recombinant expression vector is a viral vector.

36. (New) The method according to Claim 35, wherein the viral vector is delivered in a pharmaceutically acceptable composition, and provides from  $10^{10}$  to  $10^{12}$  viral particles/ml of composition.

37. (New) The method according to Claims 1 or 33, wherein the mammal is a human and the transgene encodes a human nervous system growth factor.

38. (New) The method according to Claim 37, wherein the transgene encodes nerve growth factor (NGF).

39. (New) The method according to Claim 1, wherein the transgene encodes neurotrophin 3 (NT-3).

40. (New) The method according to Claim 37, wherein the transgene encodes glial derived nerve growth factor (GDNF).

41. (New) The method according to Claim 1, wherein the transgene encodes neurturin.

42. (New) The method according to Claim 1, wherein the transgene encodes neurotrophin 4/5 (NT-4/5).

43. (New) The method according to Claim 1, wherein the transgene encodes perspephin.
44. (New) The method according to Claim 35, wherein the viral vector is an adeno-associated viral vector.
45. (New) The method according to Claim 35, wherein the viral vector is a lentiviral vector.
46. (New) The method according to Claim 1, wherein the mammal is a human with aging-related impairment.